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PATENT
Customer No.: 22,852
Attorney Docket No.: 03806.0532

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5/24/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Chin-Wen CHI et al.

Application No.: 10/083,565

Filed: February 27, 2002

For: USE OF DOCETAXEL FOR TREATING HEPATOCELLULAR CARCINOMA

Group Art Unit: 1614

Examiner: R. Cook

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This is a reply to the Examiner's Answer mailed on December 3, 2003, in response to the Appeal Brief filed in the above-referenced application. This Reply Brief is timely filed in triplicate.

response

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RESPONSE TO GROUNDS OF REJECTION (10)

In his Answer, the Examiner has maintained the rejection of claims 7-9, 12, and 16-22 as unpatentable under 35 U.S.C. § 103(a) over Broder *et al.* (U.S. Patent No. 6,245,805 B1; *"Broder"*). Present claim 7, the only independent claim, recites:

> 7. A method of treating hepatocellular carcinoma, said method comprising administering to a patient docetaxel in an amount sufficient to treat said hepatocellular carcinoma, wherein said administering is intravenous.

The claimed method requires intravenous administration of docetaxel in an amount sufficient to treat hepatocellular carcinoma. The claimed method is not directed to the oral co-administration of docetaxel and cyclosporin, as required by *Broder*. It recites intravenous administration of docetaxel alone. Although present claim 7 is "open" to other compounds, it is not open to compounds that are incompatible with intravenous administration. Because intravenous administration is claimed, one of ordinary skill in the art would not be motivated to modify *Broder* to arrive at the claimed invention as *Broder* is solely directed to oral administration. Nor would one of ordinary skill in the art be motivated to use docetaxel by itself because *Broder* specifically requires co-administration with cyclosporin.

Previously, the Examiner had admitted that *Broder* "only shows treatments with oral administration while the claims are directed to intravenous administration." (Office Action of July 30, 2002, at page 3.) Now the Examiner disregards that admission and states, as the basis of maintaining the rejection in (10) Grounds of Rejection, that

> Broder et al. discloses (col. 9, lines 7-12) that docetaxel ("heretofore administered only parenterally") is useful for treating hepatocellular carcinoma and liver metastases (col. 15, line 43). Broder additionally discloses that docetaxel is commercially available in parenteral form for

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use in a human (col. 10, lines 17-18). Broder et al further states that the dosage is from "20/1000 mg/cm^2 [sic], based on body surface area, with said daily administration continued for 1-4 consecutive days each 2-3 weeks" (col. 17, line 66 through col. 18, line 2).

The Examiner's argument is based on the careful pasting together of unrelated snippets of *Broder* and cannot be sustained. The reference to Col. 9, lines 7-12, of *Broder* actually begins at line 2 and describes the preferred embodiments of the invention as a method for increasing the oral bioavailability of paclitaxel, docetaxel, etoposide and "other drugs heretofore administered only parenterally." It is immediately clear to the skilled artisan that the focus of *Broder* is on improving oral bioavailability and oral delivery of certain antitumor agents that previously were administered parenterally.

Further, *Broder* does not link parenteral administration of docetaxel with treatment of hepatocellular carcinoma and liver metastases. Reference to Col. 15, line 43, makes clear that it is the contemplated oral administration of paclitaxel and docetaxel with an oral bioavailability enhancing drug which "may" treat hepatocellular carcinoma and liver metastases. There is absolutely no suggestion that docetaxel may be administered intravenously to treat hepatocellular carcinoma. As stated in the Appeal Brief, the emphasis has to be on the "may" of "may be treated", because, in fact, hepatocellular carcinoma had not yet been treated using oral paclitaxel, or oral docetaxel. Moreover, hepatocellular carcinoma is not identified by *Broder* as one of the cancers for which paclitaxel, even when parenterally administered, had been effective or potentially could be effective. *See Broder*, Col. 9, lines 29-40. Therefore, there is no teaching in *Broder* of oral or parenteral use of paclitaxel for this condition. If *Broder* does not teach that parenterally administered paclitaxel is effective in treating

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hepatocellular carcinoma, it cannot suggest that parenterally administered docetaxel would be effective.

Col. 10, lines 17-18, also cited by the Examiner, states that "[d]ocetaxel has become commercially available as TAXOTERE® in parenteral form for the treatment of breast cancer." At most, *Broder* suggests that docetaxel can be used parenterally in the treatment of breast cancer. The reference says nothing with respect to treating hepatocellular carcinoma with docetaxel.

Finally, the dosage amounts and mode of administration referred to by the Examiner in the Grounds for Rejection are specific to oral paclitaxel (with enhancing agent) alone. *See* Col. 17, line 64, to Col. 18, line 3. Nowhere does *Broder* disclose or suggest dosage amounts or schedules for intravenous administration of docetaxel as required by the present claims.

It is well-established that art relied upon to reject claims must be considered as a whole, and that disclosures that teach away from the claimed invention must be considered when determining obviousness. MPEP § 2145. *Broder*, as a whole, teaches a method and composition for orally administering taxanes, especially paclitaxel, which are poorly absorbed in the gut. *Broder* achieves this by co-administration of an oral bioavailability agent comprising cyclopsorin with the taxane. Broder's passing comments, taken out of context by the Examiner, that taxanes have previously been administered parenterally cannot sustain an argument that *Broder* somehow discloses parenteral (intravenous) use of docetaxel specifically in the treatment of hepatocellular cancer, especially when the reference directs the skilled

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artisan away from this direction. For these reasons, the obviousness rejection should be withdrawn.

RESPONSE TO EXAMINER'S RESPONSE TO THE ARGUMENT (11)

In the Response to the Argument (11), the Examiner states that "Broder et al disclose that docetaxel has previously been used parenterally and that in order to get sufficient absorption in order to use it orally, [docetaxel] should be administered with cyclosporin." Examiner's Answer at 4-5. The Office is reminded that oral administration of docetaxel and cyclosporin is not recited in the claims on appeal. The Examiner then states that "*Broder* et al does not teach that docetaxel should not be used parenterally." Examiner's Answer at 5. It is true that *Broder* does not make that statement but use of the double negative by the Examiner is persuasive of the opposite conclusion. It cannot be said that *Broder* teaches or suggests that docetaxel should be used parenterally and more importantly, it cannot be said that *Broder* affirmatively teaches or suggests that docetaxel should be used parenterally in the treatment of hepatocellular cancer.

The Examiner's statement at page 5, lines 10-11, of the Answer that "Broder et al discloses that docetaxel can be used to treat hepatocellular carcinoma and a dosage range that includes the instant range" is simply incorrect. As discussed above, it is oral administration of docetaxel (co-administered with cyclosporin) that is suggested might be useful in the treatment of hepatocellular carcinoma and the dosage range recited by *Broder* is specific to orally administered paclitaxel (not parenterally administered docetaxel).

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Applicants had also argued in the Appeal Brief that *Broder*, who does not discuss the intravenous use of docetaxel in treatment of hepatocellular carcinoma, could not make that use obvious by its discussion of administering oral paclitaxel with cyclosporin. Applicants also showed that attempts to treat hepatocellular carcinoma with paclitaxel were not successful. Thus, there could be no expectation, contrary to the Examiner's assertion, that the use of docetaxel for that purpose would be successful. The Examiner does not assert that Applicants' arguments are incorrect but simply that the arguments are not persuasive since "the instant claims recited docetaxel and not paclitaxel." (Examiner's Answer at 5, line 7). However, the Examiner's obviousness rejection is based on extrapolating Broder's statements about paclitaxel to docetaxel. If the Examiner contends that Applicant's arguments are not persuasive because the claims are directed to docetaxel, not paclitaxel, then the Examiner's own obviousness rejection cannot be sustained because they are based on Broder's discussion of paclitaxel. To conclude otherwise would be inconsistent.

Finally, in response to the argument that the doses disclosed by *Broder* for the oral administration of paclitaxel and cyclosporin would not suggest appropriate doses of docetaxel for intravenous administration as recited in instant claims 17-19 and 22, the Examiner points to Col. 15, lines 11-12, of *Broder* as stating that the blood level of paclitaxel reached after oral administration is comparable to that achieved with IV infusion. In fact, that sentence, when taken with the immediately preceding sentence, says that oral administration of paclitaxel at the doses given (20 mg/m^2 to 1000 mg/m^2 depending upon patient body surface area) resulted in plasma levels of paclitaxel in humans in the range of 50-500 mg/ml for 8-12 hours after each oral dose which was the

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equivalent of levels achieved with 96 hour (4 days) IV infusion of paclitaxel. This passage from Broder does not make obvious the particular intravenous dosages of the claims on appeal and moreover, recites a purported equivalence to a level of IV infusion which is not relevant to clinical use. Generally speaking, the IV protocol for paclitaxel is infusion for three hours or for 24 hours, not for 96 hours, for the very reasons cited by *Broder*, great inconvenience, discomfort, loss of time, infection potential, etc. Likewise, the claimed invention contemplates IV infusion of docetaxel for much shorter times than 96 hours. *See*, for example, claim 22, where a dose of 100 mg/m of docetaxel is infused over one hour every three weeks. The statement of equivalence cited by the Examiner in support of her contention that the oral dosages cited by *Broder* make obvious the intravenous doses cited in claims 17-19 and 22 is simply not relevant to consideration of the claims on appeal.

CONCLUSION

For all of the reasons discussed above, as well as the arguments made in the Appeal Brief and not reiterated here, Appellants respectfully submit that claims 7-9, 12 and 16-22 define patentable subject matter over *Broder*. Therefore, Appellants respectfully request that this Honorable Board reverse the rejection of claims 7-9, 12, and 16-22, and permit this application to issue as a U.S. patent.

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To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Reply Brief, such extension is respectfully requested. If there is any fee due under 37 C.F.R. § 1.16 or § 1.17 that is not submitted with this Reply Brief, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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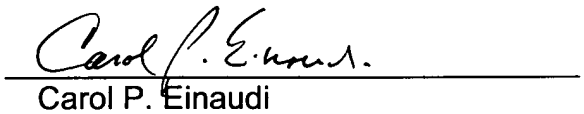
Dated: February 2, 2004

By: 

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